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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,897	03/24/2004	Rong Xiang	TSRI 874.1	6550

7590 04/25/2008

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
04/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,897	XIANG ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,26,28 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,26,28 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 March 2004 and 24 March 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 20, 2007 has been entered.

Claims 2-25, 27, and 29-52 are cancelled. Claims 1, 26, 28, and 53 are pending. Claims 1, 26, 28, and 53 are currently under examination.

This application 10/807,897 filed on March 24, 2004 claims the benefit of 60/457,009 filed on 03/24/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous rejection of claims 1, 26-29, and 53 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier, **does not** reasonably provide enablement for the said method comprising *any cytokine, is* ***withdrawn*** because the claims have been amended.

Claim 1 has been amended to read as follows: A DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut.

New Matter

3. Claims 1, 26, 28, and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* 37 CFR 1.118 (a) states that "No amendment shall introduce **new matter** into the disclosure of an application after the filing date of the application". *This new rejection is necessitated by claim amendments filed by Applicant on 07/30/2007.*

Amended independent claim 1 recites the limitation "*at least one CCL21 cytokine*". In the response filed on 07/30/2007, Applicant indicates that the claims are now amended to specify that the cytokine is a CCL21 cytokine, and notes that claims 28 and 53 were already directed to DNA constructs in which the cytokine was a CCL21 cytokine (i.e., SEQ ID NO: 7).

It is noted that the specification discloses that SEQ ID No: 7 is the nucleic acid encoding murine CCL21 and SEQ ID No: 5 is the nucleic acid encoding human CCL21. The specification discloses in Figure 10 the alignment between amino acid sequences of murine CCL21 (muCCL21) and the amino acid sequences of human CCL21 (hCCL21). However, the

Examiner notes that there are multiple species of murine animals, including mouse, rat, hamster, etc, and the specification does not disclose which species of murine animals that SEQ ID No: 7 is isolated from. Relevant to this issue, the amended limitation "at least one CCL21 cytokine" recited in claim 1 reads on multiple species of DNA sequences encoding multiple species of CCL21 cytokine being included in the DNA vaccine. In this regard, the specification does not disclose administration of multiple CCL21 cytokines encoded by the same DNA vaccine at once, which is encompassed by the amended claim limitation "at least one CCL21 cytokine" recited in claim 1.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, and a study of the entire application is often necessary to determine whether or not "new matter" is involved.

Applicant should therefore specifically point out the support for any amendments made to the disclosure.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Previous rejection of claims 1, 26, 28 and 53 under 35 U.S.C. 103(a) as being unpatentable over Rovero et al. (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185 (neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) taken with Altieri (Altieri, Validating survivin as a cancer therapeutic target. Nat Rev Cancer. 3(1): 46-54, 2003), Nagira et al. (Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), Bennett et al. (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006), Tanabe et al. (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006), is ***withdrawn*** because claims have been amended.

Claim 1 has been amended to read as follows: A DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut.

None of Rovero et al., Altieri, Nagira et al., Bennett et al., Tanabe et al. teaches the amended limitation "wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut".

5. Previous rejection of claims 1 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rovero et al. (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185 (neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) taken with Altieri (Altieri, Validating survivin as a cancer therapeutic target. Nat Rev Cancer. 3(1): 46-54, 2003), Nagira et al. (Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), Bennett et al. (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006), Tanabe et al. (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-

Final office action mailed on 12/13/2006), and Pawelek et al. (Pawelek et al., U.S. patent 6,190,657, date of patent Feb. 20, 2001; this reference has been provided in the Non-Final office action mailed on 12/13/2006), is ***withdrawn*** because claims have been amended and Applicant's argument have been fully considered and found persuasive.

Claim 1 has been amended to read as follows: A DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut.

None of Rovero et al., Altieri, Nagira et al., Bennett et al., Tanabe et al., Pawelek et al. teaches the amended limitation "wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut".

The following rejections under 35 U.S.C. 103(a) are necessitated claim amendments filed on 12/21/2007.

6. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Rovero et al.** (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185 (neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002), **Nagira et al.** (Nigira et al., A

lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), and **Lu et al.** (US 5,733,760, issued 03/31/1998). *This rejection is necessitated by the claim amendments of claim 1 filed on 12/21/2007.*

Claim 1 is drawn to a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut.

The scientific framework of claim 1 is directed to a DNA vaccine which can elicit an immune response against a tumor antigen and the immune response is boosted by a genetic cytokine adjuvant. **Rovero et al.** taught use of DNA vaccination against tumor antigens by expression of a tumor antigen and a cytokine from a DNA construct. Specifically, Rovero et al. teach an assessment of the effectiveness of DNA vaccination in prevention of the mammary adenocarcinomas of BALB/c female mice transgenic for the activated rat Her-2/neu oncogene, a breast cancer specific tumor antigen (See Abstract, page 447, Rovero et al., 2001). Rovero et al. also teach that an enhancement of the potency of DNA vaccines has been sought through the employment of cytokines as adjuvants, and vaccines encoding antigens fused with immunological molecules and cytokines elicit more effective responses and the ability of cytokines to enhance the immune recognition of tumor antigens has been extensively exploited. Specifically, Rovero et al. compared the ability of DNA vaccination with plasmids coding for the

extracellular domain of product of rat Her-2/neu ($p185^{neu}$) alone (ECD) or fused with the DNA coding for this IL-1β peptide (ECD-IL-1βp) to block the progression of Her-2/neu carcinogenesis in female BALB/c mice transgenic for the activated rat Her-2/neu oncogene under the control of the MMTV promoter (BALB-neuT). Rovero et al. reported that all the mammary glands of these mice independently undergo a very aggressive carcinogenesis that mirrors some features of the formation of lobular carcinoma in women. Vaccination with plasmids coding for ECD alone did not block this carcinogenesis, whereas vaccination with ECD-IL-1βp was followed by a significant delay in carcinogenesis (See Introduction, page 447, and Figure 1, page 448, Rovero et al., 2001).

Rovero et al. does not teach **(i)** survivin as a tumor specific antigen, **(ii)** CCL21 as a cytokine that enhance T cell mediated immune response, or **(iii)** a DNA incorporating the construct in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut.

However, at the time of filing of instant application, the art taught that (i) universal tumor antigens, including survivin, expressed in all tumors but not expressed in non-cancerous tissue, can be used as targets immunotherapy, and (ii) the tumor cell specific immune response can be enhanced by the presence of various cytokines (See, for instance, second paragraph, right column page 118, Gordan et al., 2002). Furthermore, the advantages of a vaccine comprising attenuated *Salmonella typhimurium* as a vector to express exogenous antigen(s) that can be delivered orally for vaccination and targets Peyer's patches in the gut, are also known in the art.

Regarding tumor associated antigens as targets for immunotherapy, **Gordan et al.** teaches that the cardinal feature of universal tumor associated antigen (TAA, also known as tumor specific antigen) is that they are expressed in nearly all tumors but not expressed in non-

cancerous tissue , and they are directly involved in the malignant phenotype of the tumor. Gordan et al. teaches that certain peptides derived from such Ags are expressed on the tumor-cell surface, as evidenced by Ag-specific, MHC-restricted T-cell anti-tumor reactivity. Gordan et al. also teaches that four examples of candidate universal tumor Ags, including the inhibitor of apoptosis survivin, each at various levels of preclinical and clinical development. Gordan et al. further teaches that features of universal TAA indicate a pre-existing, high-affinity T-cell pool that can be activated *in vivo* in patients, without immunoselection of variant tumor cells no longer expressing the Ag of choice. (See summary of Results and Discussion, page 317, Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002).

Regarding CCL21/SLC (secondary lymphoid tissue chemokine) as a cytokine that enhances T cell mediated immune response, **Nagira et al.** teach that secondary lymphoid tissue chemokine (SLC) is a CC chemokine expressed mainly in lymph nodes, appendix and spleen, and specifically chemotactic for lymphocytes (Nagira et al., 1998). Nagira et al. (1998) carried out transendothelial migration assays to determine the classes and subsets of lymphocytes migrating toward CCL21. CCL21 attracted freshly isolated B cells with high efficiency and T cells modestly. Thus, Nagira et al. show that CCL21 is the first CC chemokine with a strong chemotactic activity on fresh B cells. Among T cell types and subsets, Nagira et al. showed that SLC broadly attracted $CD4^+$ and $CD8^+$ cells, $CD45RO^-$ (naive) and $CD45RO^+$ (memory) cells, and $CD26^{high}$ (activated) and $CD26^{low-}$ (resting) cells. Nagira et al. (1998) further showed that SLC also attracted both L-$selectin^+$ and L-$selectin^-$ subpopulations of various T cell subsets and B cells (See Abstract, Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid

tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998).

Regarding the limitation "DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut", **Lu et al.** (1998) teaches the following: Attenuated *Salmonella typhimurium* has been proposed as one means of providing effective delivery of desired antigens. They provide the advantage that they can be delivered orally. The bacteria grow rapidly and do not require growth in cell culture. Thus, large scale production of vectors, for example, in the use of vaccines, can be accomplished more quickly and easy then where mammalian tissue cultures are required. After oral ingestion, *Salmonella* are concentrated within the liver, spleen, bone marrow, and the Peyers' patches of the gut-associated lymphoid tissue (GALT) (See Abstract, and lines 39-54, column 1, Lu et al., 1998).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to generate a DNA vaccine construct to be incorporated into and delivered by *Salmonella* vector, as taught by Lu et al (1998), via modification of the DNA vaccination construct to encode survivin as an universal tumor associated antigen, as taught by Gordan et al., and CCL21 as a cytokine, as taught by Nagira et al., 1997. It would have been obvious to replace the breast tumor specific antigen Her-2/neu ($p185^{neu}$) with non-breast cancer restricted universal tumor associated antigen survivin, taught by Gordan et al., and replace the DNA encoding cytokine IL-1β peptide taught by Rovero with DNA encoding cytokine CCL21, as taught by Nagira et al. Such a DNA construct encoding both survivin and CCL21, would elicit an immune response against various cancer cells via both activation of B cell mediated production of antibody against survivin, which is universally expressed in all tumor cells, and T

cell mediated cytolytic response enhanced by cytokine CCL21-directed immune response in a tumor cell specific manner.

One having ordinary skill in the art would have been motivated to replace the breast tumor specific antigen Her-2/neu ($p185^{neu}$) with non-breast cancer restricted tumor specific antigen survivin, taught by Gordan et al., and replace DNA encoding cytokine IL-1β peptide with DNA encodes cytokine CCL21/SLC, as taught by Nagira et al., and incorporating the DNA construct into a *Salmonella* vector because (i) survivin is universally expressed in all human tumors, and the features of universal TAA indicate a pre-existing, high-affinity T-cell pool that can be activated *in vivo* in patients, without immunoselection of variant tumor cells no longer expressing the Ag of choice, (ii) CCL21/SLC can enhance immune response against tumor specific antigen via both activation of T cells and attraction of B cells that produce antibody against survivin, which is universally expressed in all human tumor cells, and T cell mediated cytolytic response and B cell mediated immune response enhanced by cytokine CCL21 directed immune response in a tumor cell specific manner, (iii) attenuated *Salmonella typhimurium* provides effective delivery of desired antigens by oral vaccination as large scale production of attenuated *Salmonella* vectors can facilitate the vaccination process and effectiveness.

There would have been a reasonable expectation of success given (i) successful DNA vaccine construct encodes both Her2 and IL-1β in eliciting immune responses to breast cancer specific tumor antigen Her2 by the teachings of Rovero et al., and (ii) successful identification and validation of surviving as an universal tumor associated antigen as a target of cancer immunotherapy, by the teachings of Gordan et al., (iii) successful demonstration of the effect of CCL21 in increasing T cell mediated cytolytic response as well as B cell recruitment, by the

teachings of Nagira et al., and (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigens and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Rovero et al.** (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185 (neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002), **Nagira et al.** (Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), **Lu et al.** (US 5,733,760, issued 03/31/1998) as applied to claim 1 above, and further in view of **Bennett et al.** (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006).

The teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. have been discussed in the preceding section of the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Rovero et al. (2001) in view of Gordan et al. (2002), Nagira et al.(1998), and Lu et al. (1998).

None of Rovero et al., Gordan et al., Nagira et al., and Lu et al. teaches SEQ ID No: 3 recited in claim 26.

However, at the time of filing of instant application, the DNA construct encoding a murine survivin protein comprising SEQ ID No. 3 recited in claim 26, was known in the art. For instant, **Bennett et al.** teach DNA encoding mouse survivin that identical to SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, detailed alignment of sequences listed below)

```
RESULT 1

AAS21530
ID   AAS21530 standard; cDNA; 955 BP.
XX
AC   AAS21530;
XX
DT   21-NOV-2001  (first entry)
XX
DE   DNA encoding mouse survivin.
XX
KW   Survivin; human; mouse; cytostatic; antisense oligonucleotide;
KW   hyperproliferative condition; cancer; apoptosis; cytokinesis; ss.
XX
OS   Mus musculus.
XX
PN   WO200157059-A1.
XX
PD   09-AUG-2001.
XX
PF   30-JAN-2001; 2001WO-US002939.
XX
PR   02-FEB-2000; 2000US-00496694.
XX
PA   (ISIS-) ISIS PHARM INC.
XX
PI   Bennett CF,  Ackermann EJ,  Swayze EE,  Cowsert LM;
XX
DR   WPI; 2001-488863/53.
XX
PT   Novel antisense compounds for modulating the expression of Survivin and
PT   treatment of cancer.
XX
PS   Example 13; Page 80-81; 120pp; English.
XX
CC   The invention relates to antisense oligonucleotides targeted to a nucleic
CC   acid molecule encoding human Survivin, where the antisense
CC   oligonucleotide inhibits the expression of human Survivin. These
CC   antisense oligonucleotides are used in the treatment of an animal
CC   suffering from a disease or condition associated with Survivin, e.g. a
CC   hyperproliferative condition such as cancer, and comprises administering
CC   a therapeutically or prophylactically effective amount of the antisense
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CC oligonucleotide so that expression of Survivin is inhibited. The
CC oligonucleotides can also be used to treat a human suffering from a
CC disease or condition characterised by a reduction in apoptosis comprising
CC administering the antisense oligonucleotide to a human. In addition, the
CC antisense oligonucleotide and a cytotoxic chemotherapeutic agent e.g.
CC taxol or cisplatin, can be used to modulate apoptosis, cytokinesis or the
CC cell cycle, or inhibit the proliferation in a cancer cell by contacting
CC the cell with the antisense oligonucleotide. AAS21521-AAS21768 represent
CC Survivin nucleic acids, and antisense oligonucleotides targeted to
CC Survivin, used in the method of the invention.
XX
SQ Sequence 955 BP; 230 A; 227 C; 265 G; 233 T; 0 U; 0 Other;

Query Match 100.0%; Score 955; DB 5; Length 955;
Best Local Similarity 100.0%; Pred. No. 3.6e-284;
Matches 955; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GGCACGAGGGGGCCGGGGCTCTCCCGGCATGCTCTGCGGCGCGCCTCCGCCCGCGCGATT 60

Qy         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TGAATCCTGCGTTTGAGTCGTCTTGGCGGAGGTTGTGGTGACGCCATCATGGGAGCTCCG 120

Qy        121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GCGCTGCCCCAGATCTGGCAGCTGTACCTCAAGAACTACCGCATCGCCACCTTCAAGAAC 180

Qy        181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 TGGCCCTTCCTGGAGGACTGCGCCTGCACCCCAGAGCGAATGGCGGAGGCTGGCTTCATC 240

Qy        241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 CACTGCCCTACCGAGAACGAGCCTGATTTGGCCCAGTGTTTTTTCTGCTTTAAGGAATTG 300

Qy        301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GAAGGCTGGGAACCCGATGACAACCCGATAGAGGAGCATAGAAAGCACTCCCCTGGCTGC 360

Qy        361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 GCCTTCCTCACTGTCAAGAAGCAGATGGAAGAACTAACCGTCAGTGAATTCTTGAAACTG 420

Qy        421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 GACAGACAGAGAGCCAAGAACAAAATTGCAAAGGAGACCAACAACAAGCAAAAAGAGTTT 480

Qy        481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 GAAGAGACTGCAAAGACTACCCGTCAGTCAATTGAGCAGCTGGCTGCCTAATGCTGAGCC 540
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Qy        541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 TTTGCTGAGATAACTTGGACCTGAGTGACATGCCACATCTAAGCCACGCATCCCAGCTTT 600

Qy        601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 TCCAGCCAGGGCCTCCTAGCAGGATCTTAGAGAAGGAGACAGTGGTATTTTGAAACTGGA 660

Qy        661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 TATCAAATATTTTTGGTTTTGCTTTAAAGTGGCTACCTCTCTTTGGTTTTGTGGCTTTGC 720

Qy        721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 TCTATTGTGACGTGGACTTAAGCAATAAGGAAGTGATGAAGGGACAGTGTTCTCTGACAG 780

Qy        781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 GACCTGTGGGGGTCGGGGTGCCTGTGCAAGGTCTTGGTTCTGATTGTGATATTTCCATAC 840

Qy        841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 AGGGCTGCTAATGCAGCCCATGGGTAAGTGTGGTTATATGTGTTTGTGCTGATAATTTTG 900

Qy        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
              |||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 TCCTGATGAGTTTTCCTACCACGGGGTAACGGAATAAAATCACTTGAAAAAGTGG 955
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Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Bennett et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 3 recited in claim 26 of instant application, into the combined teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. directing to a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut of a patient when the patient is orally vaccinated with the DNA construct.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Bennett et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 3 recited in claim 26 of instant application, into the combined teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. because survivin is conserved in mammals, universally expressed in tumor cells but not in other normal tissues, and SEQ ID No: 3 encodes mouse survivin.

There would have been a reasonable expectation of success given (i) successful DNA vaccine construct encodes both Her2 and IL-1β in eliciting immune responses to breast cancer specific tumor antigen Her2 by the teachings of Rovero et al., and (ii) successful identification and validation of surviving as an universal tumor associated antigen as a target of cancer immunotherapy, by the teachings of Gordan et al., (iii) successful demonstration of the effect of CCL21 in increasing T cell mediated cytolytic response as well as B cell recruitment, by the teachings of Nagira et al., (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigen and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998, and (v) DNA encoding mouse survivin was readily available.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

8. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Rovero et al.** (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185 (neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens

as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002), **Nagira et al.** (Nigira et al., A lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), **Lu et al.** (US 5,733,760, issued 03/31/1998) as applied to claim 1 above, and further in view of **Tanabe et al.** (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006).

The teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. have been discussed in the preceding section of the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Rovero et al. (2001) in view of Gordan et al. (2002), Nagira et al.(1998), and Lu et al. (1998).

None of Rovero et al., Gordan et al., Nagira et al., and Lu et al. teaches SEQ ID No:7 recited in claim 28.

However, at the time of filing of instant application, the DNA construct encoding a murine survivin protein comprising SEQ ID No. 7 recited in claim 28, was known in the art. For instant, **Tanabe et al.** teach DNA encoding mouse CCL21 that is identical SEQ ID NO: 7 (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, detailed alignment of sequences listed below; this reference has been provided in the Non-Final office action mailed on 12/13/2006).

```
RESULT 1
AF006637
LOCUS       AF006637                615 bp    mRNA    linear   ROD 22-JUN-
1997
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DEFINITION  Mus musculus beta-chemokine TCA4 mRNA, complete cds.
ACCESSION   AF006637
VERSION     AF006637.1  GI:2209188
KEYWORDS    .
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Muridae; Murinae; Mus.
REFERENCE   1  (bases 1 to 615)
  AUTHORS   Tanabe,S., Lu,Z., Luo,Y., Quackenbush,E.J., Berman,M.A.,
            Collins-Racie,L.A., Mi,S., Reilly,C., Lo,D., Jacobs,K.A. and
            Dorf,M.E.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-JUN-1997) Genetics Institute, 87 Cambridge Park
            Drive, Cambridge, MA 02140, USA
FEATURES             Location/Qualifiers
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                     /organism="Mus musculus"
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                     /db_xref="taxon:10090"
                     /tissue_type="thymus"
                     /dev_stage="adult"
     CDS             97. .498
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                     /codon_start=1
                     /product="TCA4"
                     /protein_id="AAB61440.1"
                     /db_xref="GI:2209189"

/translation="MAQMMTLSLLSLVLALCIPWTQGSDGGGQDCCLKYSQKKIPYSI

VRGYRKQEPSLGCPIPAILFSPRKHSKPELCANPEEGWVQNLMRRLDQPPAPGKQSPG
                     CRKNRGTSKSGKKGKGSKGCKRTEQTQPSRG"
ORIGIN

  Query Match             100.0%;  Score 615;  DB 6;  Length 615;
  Best Local Similarity   100.0%;  Pred. No. 3e-193;
  Matches  615;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GAATTCGGCCAAAGAGGCCTACGGCCAAAGAGGGCTAAACTTGCGGCTGTCCATCTCACC 60

Qy         61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TACAGCTCTGGTCTCATCCTCAACTCAACCACAATCATGGCTCAGATGATGACTCTGAGC 120

Qy        121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 CTCCTTAGCCTGGTCCTGGCTCTCTGCATCCCCTGGACCCAAGGCAGTGATGGAGGGGGT 180

Qy        181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240
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                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 CAGGACTGCTGCCTTAAGTACAGCCAGAAGAAAATTCCCTACAGTATTGTCCGAGGCTAT 240

Qy        241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 AGGAAGCAAGAACCAAGTTTAGGCTGTCCCATCCCGGCAATCCTGTTCTCACCCCGGAAG 300

Qy        301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 CACTCTAAGCCTGAGCTATGTGCAAACCCTGAGGAAGGCTGGGTGCAGAACCTGATGCGC 360

Qy        361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 CGCCTGGACCAGCCTCCAGCCCCAGGGAAACAAAGCCCCGGCTGCAGGAAGAACCGGGGA 420

Qy        421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 ACCTCTAAGTCTGGAAAGAAAGGAAAGGGCTCCAAGGGCTGCAAGAGAACTGAACAGACA 480

Qy        481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 CAGCCCTCAAGAGGATAGCCCAGTAGCCCGCCTGGAGCCCAGGAGATCCCCCACGAACTT 540

Qy        541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 CAAGCTGGGTGGTTCACGGTCCAACTCACAGGCAAAGAGGGAGCTAGAAAACAGACTCAG 600

Qy        601 GAGCCGCTAGTCGAG 615
                |||||||||||||||
Db        601 GAGCCGCTAGTCGAG 615
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Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Tanabe et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 7 recited in claim 28 of instant application, into the combined teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. directing to a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut of a patient when the patient is orally vaccinated with the DNA construct.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Tanabe et al. on the DNA encoding mouse surviving, which is identical to SEQ ID NO: 7 recited in claim 28 of instant application, into the combined teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. because cytokine CCL21 is known to enhance T cell and B cell mediated immune response, and SEQ ID No: 7 encodes mouse CCL21.

There would have been a reasonable expectation of success given (i) successful DNA vaccine construct encodes both Her2 and IL-1β in eliciting immune responses to breast cancer specific tumor antigen Her2 by the teachings of Rovero et al., and (ii) successful identification and validation of surviving as an universal tumor associated antigen as a target of cancer immunotherapy, by the teachings of Gordan et al., (iii) successful demonstration of the effect of CCL21 in increasing T cell mediated cytolytic response as well as B cell recruitment, by the teachings of Nagira et al., (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigen and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998, and (v) DNA encoding mouse CCL21 was readily available.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

9. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Rovero et al.** (Rovero et al. Insertion of the DNA for the 163-171 peptide of IL1beta enables a DNA vaccine encoding p185 (neu) to inhibit mammary carcinogenesis in Her-2/neu transgenic BALB/c mice. *Gene Ther.* 8(6): 447-52, 2001) in view of **Gordan et al.** (Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002), **Nagira et al.** (Nigira et al., A

lymphocyte-specific CC chemokine, secondary lymphoid tissue chemokine (SLC), is a highly efficient chemoattractant for B cells and activated T cells. *Eur J Immunol.* 28(5):1516-23, 1998), **Lu et al.** (US 5,733,760, issued 03/31/1998) as applied to claim 1 above, and further in view of **Bennett et al.** (Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55; this reference has been provided in the Non-Final office action mailed on 12/13/2006), and **Tanabe et al.** (Tanabe et al., direct submission, submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, direct submission of DNA sequences of CCL21; this reference has been provided in the Non-Final office action mailed on 12/13/2006).

The teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. have been discussed in the preceding section of the rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Rovero et al. (2001) in view of Gordan et al. (2002), Nagira et al.(1998), and Lu et al. (1998).

None of Rovero et al., Gordan et al., Nagira et al., and Lu et al. teaches SEQ ID No:3 and SEQ ID No: 7 recited in claim 53.

However, at the time of filing of instant application, the DNA construct encoding a murine survivin protein comprising SEQ ID No. 3, the DNA construct encoding mouse CCL21 comprising SEQ ID No:7, recited in claim 53, were known in the art. For instant, Bennett et al. teach DNA encoding mouse survivin that identical to SEQ ID NO: 3 (See Bennett et al. WO200157059-A1 and U.S. Patent No. 6,335,194, SEQ ID No: 10, columns 27, 53-55, see detailed alignment of sequences listed in the preceding rejection #7), and Tanabe et al. teach DNA encoding mouse CCL21 that is identical SEQ ID NO: 7 (Tanabe et al., direct submission,

submitted to Genetics Institute, 87 Cambridge Park Drive, Cambridge, MA 02140, USA, on 03-JUN-1997, detailed alignment of sequences listed in the preceding rejection #8)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Bennett et al. on the DNA encoding mouse survivin, which is identical to SEQ ID NO: 3, and the teachings of Tanabe et al. on the DNA encoding mouse CCL21, which is identical to SEQ ID NO: 7, as recited in claim 53 of instant application, into the combined teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al., directing to a DNA vaccine suitable for eliciting an immune response against cancer cells comprising a DNA construct operably encoding at least one survivin protein and at least one CCL21 cytokine in a pharmaceutically acceptable carrier; wherein the DNA construct is incorporated in an attenuated *Salmonella typhimurium* vector that targets Peyer's patches in the gut of a patient when the patient is orally vaccinated with the DNA construct.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Bennett et al. on the DNA encoding mouse surviving, which is identical to SEQ ID NO: 3, and the teachings of Tanabe et al. on the DNA encoding mouse CCL21, which is identical to SEQ ID NO: 7, as recited in claim 53 of instant application, into the combined teachings of Rovero et al., Gordan et al., Nagira et al., and Lu et al. because (i) survivin is conserved in mammals, universally expressed in tumor cells but not in other normal tissues, and SEQ ID No: 3 encodes mouse survivin, and (ii) cytokine CCL21 is known to enhance T cell and B cell mediated immune response, and SEQ ID No: 7 encodes mouse CCL21.

There would have been a reasonable expectation of success given (i) successful DNA vaccine construct encodes both Her2 and IL-1β in eliciting immune responses to breast cancer

specific tumor antigen Her2 by the teachings of Rovero et al., and (ii) successful identification and validation of surviving as an universal tumor associated antigen as a target of cancer immunotherapy, by the teachings of Gordan et al., (iii) successful demonstration of the effect of CCL21 in increasing T cell mediated cytolytic response as well as B cell recruitment, by the teachings of Nagira et al., (iv) successful generation of attenuated *Salmonella typhimurium* that can express exogenous antigen and the demonstration of using attenuated *Salmonella typhimurium* for oral vaccination, by the teachings of Lu et al., 1998, and (v) DNA construct encoding mouse survivin and DNA construct encoding mouse CCL21 were readily available.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Response to Applicant's arguments

The Examiner notes that the instant application is withdrawn because of claims amendments filed on 12/20/2007 as indicated above.

(i) Applicant's arguments that the replacement of the feature of the primary reference Rovero et al. with different components, and rebuilding of the vaccine is non-inventive act of one of ordinary skill in the art, have been fully considered and found not persuasive. It is emphasized that Rovero et al. teaches the framework of instant invention with respect to induced immune response against a tumor antigen and the immune response boosted by a genetic cytokine adjuvant. Replacing the tumor antigen Her-2/neu, as taught by Rovero et al., with survivin, as taught by Gordan et al., and Bennett et al., and replacing cytokine IL1b, as taught by Rovero et al., with CCL21, as taught by Nagira et al., and Tanabe et al. have been established as *prima facie* obvious in the preceding rejections under 35 U.S.C. 103(a) in this office action.

(ii) Applicant's arguments that the DNA vaccine taught by Rovero et al. only induces antibody immune response, but does not induce significant cytotoxic T lymphocytes (CTL) immune response, have been fully considered and found not persuasive. In this regard, it is noted that claim 1 only requires "an immune response against cancer cells" and the antibody against Her-2/neu breast cancer tumor antigen is encompassed by the immune response recited in claim 1. Furthermore, the cited reference Gordan et al. teaches that the cardinal feature of universal tumor associated antigen (TAA, also known as tumor specific antigen) is that they are expressed in nearly all tumors and in no normal tissues, and they are directly involved in the malignant phenotype of the tumor. Gordan et al. teaches that certain peptides derived from such Ags are expressed on the tumor-cell surface, as evidenced by Ag-specific, MHC-restricted T-cell anti-tumor reactivity. Gordan et al. also teaches that four examples of candidate universal tumor Ags, including the inhibitor of apoptosis survivin, each at various levels of preclinical and clinical development. Gordan et al. further teaches that features of universal TAA imply a pre-existing, high-affinity T-cell pool that can be activated *in vivo* in patients, without immunoselection of variant tumor cells no longer expressing the Ag of choice. (See summary of Results and Discussion, page 317, Gordan et al. Universal tumor antigens as targets for immunotherapy, *Cytotherapy*, 4(4):317-27, 2002).

(iii) Applicant argues that Pawelek et al. disclose different *Salmonella typhimurium* strains. The Pawelek et al. strains have been selected to be super-infective toward tumor cells (see col. 7, lines 50-65, and col. 31-39, Examples 7.2, 8, and 9, which describe the isolation of super-infective, tumor-specific *Salmonella typhimurium*), however, the presently claimed vaccines utilize attenuated *Salmonella typhimurium* that target the Peyer's patches; in the gut,

rather than tumor cells directly. Applicant further argues that one of ordinary skill in the art would not have been motivated to incorporate the hypothesized, highly modified Rovero vaccine (i.e., comprising DNA encoding survivin and CCL21), into an attenuated *Salmonella typhimurium* that targets Peyer's patches, based on the disclosure in Pawelek el al, regarding different *Salmonella typhlmurium* strains, which are super-infective and which target tumor cells.

In response, Applicant's arguments have been fully considered and found persuasive. Accordingly, previous rejection of claims 1 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rovero et al. in view of Altieri, Nagira et al. , Bennett et al., Tanabe et al. and Pawelek et al. is ***withdrawn*** in this office action.

Conclusion

10. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1632

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Primary Examiner
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